Metabolic side effects of second generation antipsychotics: a comparative cross-sectional study

In partial fulfillment of the post graduate program in psychiatry

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Table of contents

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List of abbreviation

BP- Blood pressure

BMI- Body mass index

DM- Diabetes mellitus

DKA- Diabetic ketoacidosis

FBS –Fasting blood sugar

FGAs- First generation antipsychotics

HDL- High density lipoprotein

IDF- International Diabetes Federation (IDF)

MS- Metabolic syndrome

NCEP ATPIII- National Cholesterol Education Program Adult Treatment Panel III

SGAs- Second generation antipsychotics

SMI- Severe mental illness

TG- Triglycerides

WC - Waist circumference

WHO- World Health Organization

Abstract

Background

There is evidence that people with mental illness are more likely to suffer from metabolic syndrome compared to the general population, especially those taking second generation antipsychotics (SGAs). However, there is dearth of data comparing the metabolic side effects of first generation and second generation antipsychotics. SGAs are also newly introduced in the Ethiopian setting. The objective of this study was to explore the potential metabolic side effect of SGAs.

Method

Design: A cross sectional study, comparing the prevalence of metabolic syndrome in patients with severe mental illness taking FGAs or SGAs (for at least 6weeks)
Setting: Study was conducted at Amanuel Specialized Mental Hospital in Ethiopia and participants were recruited from the inpatient departments.
Participants: An initial sample size of 150 was required for the detection of a 50% difference in the rate of metabolic syndrome between SGAs and FGAs at a 1:1 allocation ratio. However, only one hundred participants were recruited because SGAs were often running out off stock and took longer than anticipated to get adequate number on SGAs. However, candidate believes 100 participants would be adequate for this kind of exploratory and hypothesis generating study.
Measurement: Data on basic demographics, including relevant family history, dietary habit, clinical information (diagnosis, duration of illness and medication) and metabolic profile was collected. Diagnosis of metabolic syndrome was made according to the criteria of the International Diabetes Federation.
Analysis: Focused on simple descriptive approaches with limited bivariate analysis.

Result

In the 4month study period 100 participants were included, who fulfilled the inclusion criteria. For ease of access, all participants were inpatients. Sixty six percent (n=66) were male and 34% (n=34) were female. The mean age of the patients was 31.1years (SD 9.7). Fifty four (n=54) percent of the participants were prescribed SGA and 46 of the participants were prescribed FGA. According to IDF criteria 8.5% (n= 8) met the diagnostic criteria for metabolic syndrome. The prevalence of metabolic syndrome in FGA group was 2.3% and SGA group was 14%. (Crude OR= 7; 95% CI = 0.82, 59.3; P = .074).

Conclusion

Overall, the prevalence of metabolic syndrome is relatively low, especially among those taking FGAs. Although the study failed to find statistically significant difference between those taking SGAs and FGAs, there was a strong trend of association between SGAs and metabolic syndrome.

Further confirmatory studies are required; however, taken together with the broader literature regarding SGAs and metabolic syndromes, careful screening and monitoring has to be part of standard clinical practice.

Introduction

Background

Antipsychotic medications are important components in the medical management of many psychiatric disorders, especially severe mental illnesses such as schizophrenia and bipolar disorders. Since the late 1980s new antipsychotic agents with different mechanisms of action have been developed and widely adopted in the treatment of psychotic disorders. (1)

Antipsychotic drugs are classified as, first generation (also described as typical, classical, conventional) and second generation (also called novel, second generations, atypical) agents. First generation Antipsychotics (FGA) activity is derived from inhibition of dopaminergic neurotransmission and they are effective when approximately 60% of D_2 receptors in the brain are occupied. At 80 % one sees the beginning of extrapyramidal and endocrine effects like increase in prolactin levels ultimately resulting in high rate of relapse. (3)

Second generation antipsychotics are associated with lower risk of extrapyramidal side effects. They act by dual serotonin and dopamine antagonism. Nevertheless, adverse metabolic effects such as hyperglycemia, diabetes mellitus, lipid abnormalities have been increasingly recognized with the use of these newer antipsychotics. (2, 3)

Recognition of an association between SGAs and diabetes was first derived from case reports of severe, sometimes fatal, acute diabetic decompensation, including diabetic ketoacidosis (DKA). Subsequent drug surveillance and retrospective database analyses

suggest there is an association between specific SGAs and both diabetes and obesity. (4)

There is heightened interest in the relationship between the SGAs and the development of major cardiovascular disease (CVD) risk factors (obesity, diabetes, and dyslipidemia). This potential relationship is of considerable clinical concern because obesity and diabetes are important risk factors for CVD, and the relative risk of CVD mortality is significantly greater in people with psychiatric disorders than in the general population. Therefore, if SGA therapy further increases the risk for obesity and type 2 diabetes, this should be of major clinical concern. (4)

Worldwide, individuals with severe mental illnesses (SMI) such as Schizophrenia and related disorders, have a consistently higher prevalence of metabolic syndrome (MS) than the general population. The increased prevalence of MS in individuals with SMI has been attributed to several factors including the mental illness itself, the adverse effects of antipsychotic medication and traditional risk factors for CVD and type 2 diabetes mellitus such as obesity, unhealthy high fat low fibre diets, physical inactivity and smoking, which are common in patients with SMI. (5)

Three definitions of MS have been proposed by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII), the World Health Organization (WHO) and the International Diabetes Federation (IDF). Regardless of the criteria, five domains, are thought to comprise MS—large waist circumference (WC; as indicator of

central obesity), elevated triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C) concentration, high blood pressure and elevated fasting plasma glucose.

Statement of the problem

With the introduction of the second-generation antipsychotics (SGAs) over the last decade, the use of these medications has soared. Although the SGAs have many notable benefits compared with their earlier counterparts, their use has been associated with reports of dramatic weight gain, diabetes (even acute metabolic decompensation, e.g., diabetic ketoacidosis [DKA]), and an atherogenic lipid profile (increased LDL cholesterol and triglyceride levels and decreased HDL cholesterol). (4)

In many psychiatric patients the risk factors, which are an integral part of metabolic syndrome, are rarely controlled. They are often underestimated and insufficiently treated. There is evidence that people with mental disorders are more likely to suffer from metabolic syndrome. (6)

Data from most studies suggest that the prevalence of both diabetes and obesity among individuals with schizophrenia and affective disorders is 1.5–2.0 times higher than in the general population. (4)

Most evidence shows that the risk of developing MS is higher with taking SGAs compared to FGAs. A systematic review and meta-analysis showed the relative risk of developing diabetes in schizophrenic patients taking second generation compared to patients taking first generation antipsychotics was 1.32. (7)

Even though most research has focused on schizophrenia patients with bipolar disorder who are treated with SGAs have similarly high rates of MS (8). Based on a meta-analysis involving 37 studies of patients with bipolar disorders, the estimated weighted mean prevalence rate of metabolic syndrome was 37.3%. Tunisia was the only African country with a mean prevalence of 30.0%. (9)

The need for screening, monitoring and prevention of diabetes and other cardiovascular disease risk factors has been acknowledged in the psychiatric literature and in some of the more recent general treatment guidelines. However, the evaluation of screening practices by clinicians has consistently shown that they are suboptimal. Different national and international groups have developed guidelines relating to the monitoring and management of the increased risk for physical comorbidity in people with schizophrenia. (10)

There is evidence of poor screening and monitoring cardiovascular risk factors in psychiatric populations in sub-Saharan countries including Ethiopia (5, 12). Moreover, there are few or no research on the prevalence of MS in psychiatry population in this region.

Recent research on MS in the general population has indeed provided evidence for the development of ethnic-/race-specific criteria (11). However, until now, it has remained unclear to what extent these differences in the general population are due to genetic factors or cultural factors such as life style or economic factors. (11). Life style and economic factors are different between cultural and/or ethnic groups, which could

influence the prevalence of MS in a general population or patients with SMI taking antipsychotics. Therefore, identifying the prevalence of MS in different groups is needed.

Literature review

Antipsychotics are important in the management of severe mental illness but side effects associated with these medications increases the morbidity and mortality.

A prospective interventional study conducted at the Psychiatric Centre, Jaipur, India, showed 11.66% of the patients developed metabolic syndrome after 4 months of antipsychotic medication. The study included 120 patients, indoor and outdoor, suffering from schizophrenia diagnosed using the ICD-10 criteria. (13)

Comparative evaluation of EPS and other side effects made between FGAs and SGAs in 60 patients with various psychotic problems at Punjab Institute of Mental Health, Lahore, Pakistan, showed EPS occurrence was much higher in patients receiving FGAs (73%) compared to patients taking SGAs (27%). Other side effects caused by SGAs were weight gain and amenorrhea. (2)

The overall prevalence of metabolic syndrome among patients with Schizophrenia in Palestine, based on National Cholesterol Education Program Adult Treatment Panel III Adapted criteria was 43.6%, with 39% in male and 55.9% in female patients. Univariate analysis showed that MS was significantly higher with older age, female gender, longer duration of the illness, smoking, abdominal obesity, high systolic and diastolic blood pressure, high triglycerides, low HDL-C, and high fasting plasma glucose. Multiple logistic regression analysis showed that only systolic blood pressure, high triglycerides, high fasting plasma glucose, and low HDL-C were significant predictors of MS in schizophrenic patients. (11)

In Spain, a 12-week randomized, open label clinical trial evaluated metabolic changes in drug-naive, first-episode psychosis patients treated with haloperidol, olanzapine, or risperidone. 128 patients were evaluated A significant weight gain was observed with the 3 antipsychotics: haloperidol = 3.8 kg, olanzapine = 7.5 kg, and risperidone = 5.6kg. Metabolic parameters showed a worsening lipid profile with the 3 treatments. Only the olanzapine group showed significant increases in triglyceride levels. After the 12-week study period, there were no significant changes in parameters involving glucose metabolism for any group. (14)

Population based nested casecontrol study based General Practice in United Kingdom , assessed the independent effect of olanzapine and risperidone on risk of diabetes among patients with Schizophrenia: Patients taking olanzapine had a significantly increased risk of developing diabetes than nonusers of antipsychotics (odds ratio 5.8) and those taking conventional antipsychotics (4.2, 1.5 to 12.2). Patients taking risperidone had a nonsignificant increased risk of developing diabetes than nonusers of antipsychotics (2.2, 0.9 to 5.2) and those taking conventional antipsychotics (1.6, 0.7 to 3.8). (1)

In a case-control study of 90 people treated with antipsychotics in the community in UK. The prevalence of metabolic syndrome and 10-year cardiovascular risk were calculated. People on antipsychotics had a significantly worse metabolic profile than controls. Moreover, metabolic syndrome was more prevalent (OR=3.68), as was cardiovascular

risk across a number of outcomes. These results are consistent across diagnostic groups. (15)

Metabolic syndrome in patients attending psychiatric day centres in Ireland: 55% met the criteria for metabolic syndrome. There were similar prevalence rates between those with psychotic and non-psychotic disorders. 44% of the patients had not been screened for metabolic parameters in the previous 12 months, and 43% of these met criteria for metabolic syndrome. (17)

Patients with bipolar disorder and schizophrenia who are treated with SGAs have similarly high rates of MS. These findings suggest a shared susceptibility to antipsychotic-related metabolic dysregulations that is not primarily related to psychiatric diagnosis or concomitant mood stabilizer treatment. (8)

Metabolic syndrome in bipolar disorder: a cross-sectional assessment of a Health Management Organization database was performed and compared to the general population. MS prevalence was significantly higher (24.7% versus 14.4%) with no statistically significant differences between genders. All MS components were higher in the BD group, particularly BMI >28.8 kg/m^2 (versus 17.9%), high triglyceride levels (23.0% versus 11.3%), low HDL cholesterol levels (54.5% versus 29.4%), higher frequency of obesity (41.4% versus 27.1%). (16)

In a cross-sectional study done in North of England, authors investigated whether FGAs or SGAs induce a greater degree of metabolic dysfunction. Metabolic parameters were determined in 103 diagnostically heterogeneous psychiatric outpatients who had been

taking FGAs or SGAs for at least 6 months. The authors conclude that patients taking SGAs are more prone to abnormalities in glucose homeostasis. Metabolic parameters, including beta cell function and insulin sensitivity, did not differ with regard to the prescribed antipsychotic drug. Six patients had undiagnosed diabetes, six patients had impaired fasting glucose, and eight fulfilled criteria for the metabolic syndrome, all of whom were taking atypical agents (p=0.07 vs typical agents). (18)

A prospective study focusing on metabolic disturbances in patients with schizophrenia. The prevalence of metabolic abnormalities at baseline was assessed in a cohort of 415 patients with schizophrenia. The sample was divided into 4 groups according to duration of illness. Metabolic abnormalities were already present in first-episode patients, and considerably increased with increasing duration of illness (19).

Newly admitted adults treated with second-generation antipsychotics underwent assessments evaluating antipsychotic polytherapy, and of the presence of metabolic syndrome and triglycerides/high-density lipoprotein cholesterol ratio >3.5 (TG/HDL). Compared with antipsychotic monotherapy, polytherapy was associated with elevated rates of metabolic syndrome (50.0% vs. 34.3%, p=0.015) and TG/HDL (50.7% vs. 35.0%, p=0.016). (20)

There are few reports on the prevalence of MS in patients taking antipsychotic in African countries. To our knowledge there is no research carried out regarding this issue in Ethiopia.

Objective

Primary objective: To determine the excess burden of metabolic syndrome due to SGAs by comparing the prevalence of metabolic syndrome among patients taking SGAs and FGAs.

Secondary objectives:

1. To determine the prevalence of metabolic syndrome among patients taking SGAs
2. To determine the prevalence of metabolic syndrome among patients taking FGAs
3. To explore the prevalence of individual components or criteria of the metabolic syndrome among those taking SGAs and FGAs.

Hypothesis:

Overall prevalence of metabolic syndrome will be low in this sample of patients with schizophrenia and bipolar disorder recruited from Amanuel hospital, but the prevalence will be higher, by at least 10%, among those taking SGAs.

Methods

Study design

Cross sectional comparative study

Study setting

The research was conducted at Amanuel Specialised Mental Hospital, Addis Ababa, Ethiopia. Amanuel hospital is the only hospital in the country with an expanded in patient care. It has around 280 beds, a 24hr emergency service and an outpatient service. The annual case load is around 150,000 patients. Even though there are other psychiatric services within Addis Ababa and other parts of the region, most patients with severe mental illnesses visit Amanuel hospital. Antipsychotics are commonly used in the management of patients. The widely available SGAs are olanzapine and risperidone.

Source population

All patients attending Amanuel hospital during the study period

Inclusion criteria

- Both men and women, aged 18 and above
- Established diagnosis of a severe mental illness
- On antipsychotic medications for at least 6weeks prior to recruitment

- On equivalent doses of 5mg haloperidol or 300mg CPZ or 5mg of olanzapine
- Evidence of compliance for at least 50% of the time when they were taking their medication in the previous one month.

Sample size estimation

Because of the lack of data on the differential prevalence of metabolic syndrome between patients taking FGAs and SGAs in Ethiopia, we assumed the overall prevalence of metabolic syndrome among those taking SGAs to be 50%. We also assumed the prevalence of metabolic syndrome to be about 50% less (i.e., 25%) among those on FGAs. We estimated sample size for two-sample comparison of proportion, using the Stata programme, version 13. At 80% power and a 2-sided α of 0.05, the required sample size to detect a 50% difference (50% for SGA and 25% for FGA) and assuming a 10% non-response, the required sample size will be 150 patients. It was not possible to reach the estimated sample size during the actual study. This was because SGAs were out-off often during the study period making recruitment for the study difficult. Given this challenge and the time limit for the post-graduate research, only 100 patients who fulfilled the inclusion criteria were included during the 4 month period of recruitment. Although this number is well below the required sample estimation, the candidate believes that this number would be sufficient for an exploratory, hypothesis-generating study

Sampling procedure

Patients on SGAs were consecutively recruited, while patients on FGAs were recruited along with SGA patients. For each patient on SGA recruited, an unmatched comparison patient on FGAs was recruited from the inpatient setting was recruited.

Measurement

Questionnaire containing basic questions, such as, socio-demographic characteristics of the patient (age, sex, marital status, social position) and personal and family history of cardiovascular diseases and risk factors was used. Ethiopian food frequency habit questionnaire was used to obtain information about the participants' diet. The participants' charts were reviewed to get information about, their diagnosis, the duration of illness, the type of antipsychotic their taking and other clinical information. Weight, height and waist circumference were measured for all participants. Laboratory sample were obtained from all participants to measure FBS, HDL and triglycerides. HDL and triglycerides measurements were not available for all patients.

To diagnose metabolic syndrome the International Diabetes Federation (IDF) updated in 2006 was used (Box 1).

Increased waist circumference, men ≥94 cm in women ≥ 80cm

PLUS any two of the following

- Triglycerides ≥150 mg/dL or treatment for elevated triglycerides
- HDL cholesterol <40 mg/dL in men or <50 mg/dL in women, or treatment for low HDL
- Systolic blood pressure ≥130, diastolic blood pressure ≥85, or treatment for hypertension
- Fasting plasma glucose ≥100 mg/dL or previously diagnosed type 2 diabetes; an oral glucose tolerance test is recommended for patients with an elevated fasting plasma glucose, but not required

Box 1: The International Federation Criteria for Metabolic Syndrome

Data collection procedure

Patients' charts were screened to evaluate preliminary eligibility. Questionnaires were administered, after participants agreed to participate and once inclusion criteria were fulfilled. Blood pressure, weight, height and waist circumference were measured by psychiatry nurses. Most of the clinical data were retrieved from the chart. Results of laboratory investigations were used for the laboratory data.

Data analysis

Before commencing data analysis, an extensive series of checks were performed for data consistency, proper sequences of data, and an evaluation of missing or incomplete data.

Descriptive statistics for all study variables were computed. Univariate analysis was carried out using the Binary logistic regression. All statistical analyses were conducted using Statistical Package for Social Sciences (SPSS) statistical packages for Window, version 20.

Ethical consideration

Ethical approval was obtained from the Scientific Committee of the Department of Psychiatry, College of Health Sciences, AAU and from the ethical review committee of Amanuel Mental Specialized Hospital. All participants who were included in the study were asked to give informed consent before giving information.

The findings were communicated with patients and their treating physician. Participants were educated about metabolic side effects, life style modification and treatment.

Results

Demographic characteristics

In the 4month study period 100 participants were included, who fulfilled the inclusion criteria. For ease of access, all participants were inpatients. Sixty six percent (n=66) were male and 34% (n=34) were female. The mean age of the patients was 31.1years (SD 9.7). Majority of the participant were between the age of 25 and 34 and single. Most participants were from the capital city, Addis Ababa (56%). Forty percent (n=40) of the participants attended elementary school. Only 17% (n=17) either finished higher education or quit before finishing. Majority of the participants were unemployed (60%). Of the 100 participants 58 gave response regarding their own or their family's monthly income. The minimum and maximum monthly income per month was around $4.9 and $287 respectively. The median monthly income was $47.62 (Q1-Q3; 38.2-95.7). All 100 participants responded about their perceived relative wealth; 58% (n=58) thought it was low and none of the participant thought it was high. (Table 1)

Table 1: Demographic characteristics

Variables	Number	percent
Gender		
Male	66	66.0
Female	34	34.0
Age group		
Less than 25	19	19.0
Between 25 and 34	51	51.0
Between 35 and 44	23	23.0
45 and above	7	7.0
Region		
Addis Ababa	56	56.0
Oromiya	21	21.0
SNNPR	12	12.0
Amhara	10	10.0
Harari	1	1.0
Marital status		
Single	53	53.0
Married	22	22.0
Divorced/widowed	14	14.0
Cohabitation	11	11.0
Level of education		
Illiterate	8	8.0
Elementary school	40	40.0
secondary school	36	36.0
Higher education	16	16.0
Occupation		
Unemployed	60	60.0
Employed	40	40.0
***Monthly income (n=66)**		
Less than $87	46	46.0
Above $87	20	20.0
Perceived relative wealth		
Low	58	58.0
Average	42	42.0

* low income economies are defined as those with gross national income per capita calculated using the world bank atlas method of $1045 or less.

Illness and treatment characteristics

Fifty five percent (n=55) of the participants had a diagnosis of schizophrenia, 22.0% (n=22) had bipolar I disorder , 4.0% percent (n=4) had Major depressive disorder with psychotic feature and 19.0%(n= 19) of the participants had other psychotic disorder, which included 13 patients with a diagnosis of schizophreniform disorder, two participants with psychotic disorder NOS , two patients with a diagnosis of schizoaffective disorder, one participant with a diagnosis of substance induced psychosis and one participant with psychosis secondary to epilepsy. The median duration of illness was 208 weeks (Q1-Q3; 77-455). Although not confirmed during physical examination for this study, one participant reported having hypertension and another participant reported having unspecified cardiac illness. None of them were on treatment. Seven participants had family history of hypertension and three participants had family history of diabetes.

Table 2 Diagnosis

Diagnosis	Frequency	Percent
Schizophrenia	55	55.0
Bipolar I disorder	22	22.0
Other psychotic disorder	19	19.0
Major depressive disorder	4	4.0
Total	**100**	**100.0**

Fifty four percent (n=54) of the participants were prescribed second generation, risperidone(41,41.0%) and olanzapine (13,13.0%). Forty six percent (n= 45) of the

participants were prescribed first generation antipsychotic. Most commonly prescribed first generation antipsychotic was chlorpromazine (21, 21.0%) (Figure 1). Twenty percent of the participants were prescribed one additional antipsychotic. Psychotropic medications other than antipsychotics were also prescribed. Twenty eight percent (n=28) were prescribed mood stabilizers. Most commonly prescribed mood stabilizer was valproate (26, 26.0%). Eighteen percent (n=18) of the participants were on antidepressant. Thirty five percent (n=35) of the participants were on sedatives (clonazepam, diazepam and promethazine). Additionally, 13.0% of the participants were on anticholinergics and one participant with epilepsy was on phenobarbitone.

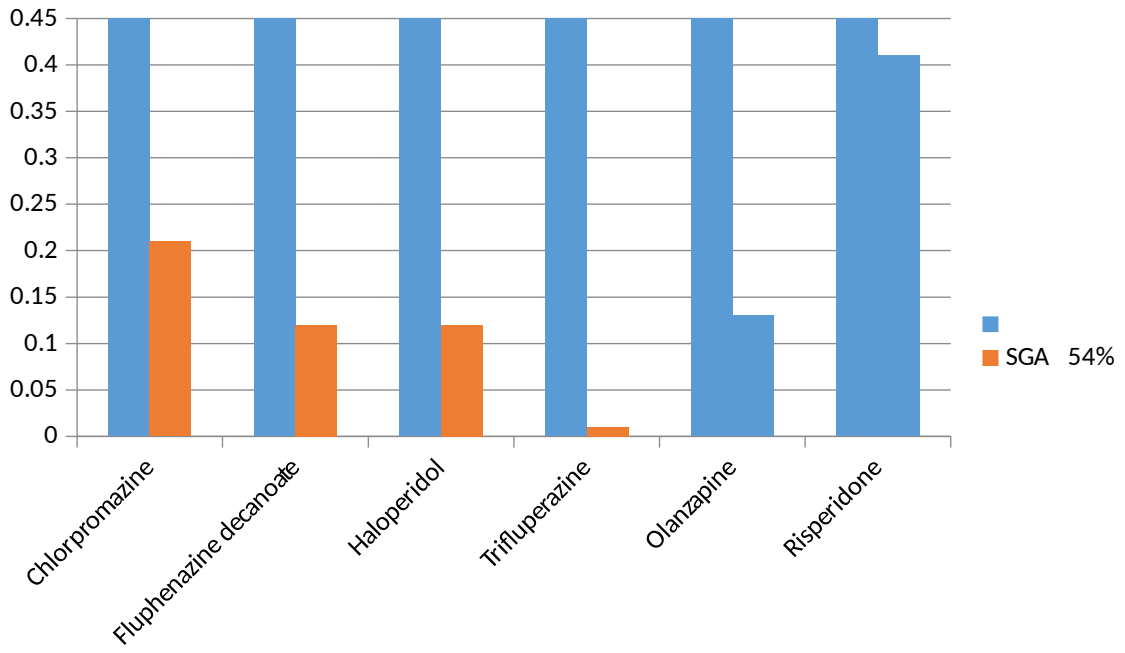

Figure 1: Percentage of participants on specific antipsychotic regimen (the antipsychotic presented here is the primary antipsychotic)

Body mass index

Body mass index of the majority participants were in the normal range (n=65; 65.0%). The prevalence of overweight and obesity were 10.0% and 8.0% respectively. Compared to participants with a diagnosis of psychotic disorder, participants with mood disorder had higher body fat mass (p= .01). There was no significant association between the type of antipsychotic patient received and higher body fat mass (Table 3).

Table 3: Body composition of participants

Characteristics		BMI(kg/m^2) defined					
		Under-weight	Normal range	Over-weight	Obese	total	P value
Gender	Male	11(16.7 %)	47(71.2 %)	5(7.6%)	3(4.5%)	66(100 %)	0.17
	Female	6(17.6%)	18(52.9 %)	5(14.7 %)	5(14.7 %)	34(100 %)	
Type of antipsychotic	FGA	8(17.4%)	31(67.4 %)	3(6.5%)	4(8.7%)	46(100 %)	.75
	SGA	9(16.7%)	34(63%)	7(13%)	4(7.4%)	54(100 %)	
Diagnosis	Mood disorder	3(11.5%)	13(50%)	4(15.4 %)	6(23.1 %)	26(100 %)	0.01
	Psychotic disorder	14(18.9 %)	52(70.3 %)	6(8.1%)	2(2.7%)	74(100 %)	

BMI- body mass index
FGA-first generation antipsychotic
SGA- second generation antipsychotics

Metabolic syndrome

Participants with diagnosis of mood disorder were likely to receive second generation antipsychotic (OR= 3.9; 95% CI=1.4, 10.9; p= .009). Abdominal obesity, abnormal lipid profile, abnormal blood pressure and abnormal blood sugar level were not significantly associated with the type of antipsychotic the participants received. (Table 4)

Table 4: Gender, diagnosis and metabolic risk by type of

Variables		Type of antipsychotics			
		FGA	SGA	Crude OR (CI 95%)	P value
Gender	Male	36(54.5%)	30(45.5%)	.35(.14-.84)	.019
	Female	10(29.4%)	24(70.6%)		
Diagnosis	Mood disorders	6(23.1%)	20(76.9%)	3.9(1.4-10.9)	.009
	Psychotic disorders	40(54.1%)	34(45.9%)		
Waist circumference for male(n=66)	≥ 94cm	6(60.0%)	4(40.0%)	.77(.19-3.02)	.71
	¿ 94cm	30(53.6%)	26(64.4%)		
Waist circumference for Female(n=34)	≥ 80cm	9(40.9%)	13(59.1%)	7.6(.83-69.9)	.073
	¿ 80 cm	1(8.3%)	11(91.7%)		
Systolic BP	≥ 130mmhg	2(33.3%)	4(66.7%)	.57(.09-3.3)	.52
	¿ 130mmhg	44(46.8%)	50(53.2%)		
Diastolic BP	≥ 85mmhg	4(57.1%)	3(42.9%)	1.6(.34-7.6)	.54
	¿ 85mmhg	42(45.2%)	51(54.8%)		
Fasting serum Tg level(n=87)	≥ 150mg/dl	13(44.8%)	16(55.2%)	1.0(.41-2.5)	1.0
	¿ 150mg/dl	26(44.8%)	32(55.2%)		
Fasting blood sugar level	≥ 100mg/dl	6(33.3%)	12(66.7%)	.52(.18-1.5)	.24
	¿ 100mg/dl	40(48.8%)	42(51.2%)		
Fasting serum HDL for male(n=54)	≥ 40mg/dl	26(52.0%)	24(48.0%)	.31(.03-3.2)	.32
	¿ 40mg/dl	1(25.0%)	3(75.0%)		

Fasting serum HDL for female(n=23)	≥ 50mg/dl	7(33.3%)	14(66.7%)	.00	.99
	¿ 50mg/dl	0	2(100.0%		

FGA- First generation antipsychotic BP-Blood pressure Tg- Triglyceride

SGA- Second generation antipsychotics HDL- High density lipoprotien

percent (n=56) of the participant had at least one abnormal parameter of the metabolic syndrome diagnostic criteria (Table 5). The prevalence of metabolic syndrome in FGA group was 2.3% and SGA group was 14% (Crude OR= 7; 95% CI 0.82, 59.3; P = .074)

Table: 5 Prevalence of metabolic syndrome using international diabetic federation diagnostic criteria for metabolic syndrome

Number of MS criteria	Frequency	Percent
0	44	44.0
1	32	32.0
2	15	15.0
3	9	9.0
4	0	0.0
5	0	0.0

MS- metabolic syndrome

Univariate analysis showed that being female (Crude OR= 7.3; 95%CI= 1.4, 38.8; p=.019) and diagnosis (Crude OR= 0.82; 95%CI= .15, .44; p=.004) were significantly associated with presence of metabolic syndrome.

Presence of metabolic syndrome were not significantly associated with age, marital status, higher education, being employed, monthly income above $87, average perceived relative wealth, longer duration of illness, taking second generation antipsychotics, taking one additional antipsychotic were , and being on mood stabilizer. (Table

Table 6: Univariate analysis of metabolic syndrome

Variable	With MS N (%)	Without MS N (%)	Crude OR (CI 95%)	P value
Age group in years				
Less than 25	1(5.6%)	17(94.4%)	3.4(.18-64.7)	.415
Between 25 and 34	5(62.5%)	43(50%)	1.72(.17- 17.8)	.649
Between 35 and 44	1(12.2%)	21(24.4%)	4.2(0.22-79.3)	.338
Above 45	1(12.5%)	5(5.8%)		
Gender				
Male	2(3.2%)	61(96.8%)	7.3(1.4-38.8)	.019
Female	6(19.4%)	25(80.6%)		
Marital status				
Married	3(16.7%)	15(83.3%)	0.35(.08- 1.6)	.183
Single	5(6.6%)	71(93.4%)		
Education				
Higher education	2(12.5%)	14(87.5%)	1.7(.3- 9.4)	.534
Primary education	6(7.7%)	72(92.3%)		
Occupation				
Employed	4(10.8%)	33(89.2%)	1.6(.38-6.9)	.523
Unemployed	4(7.0%)	53(93.0%)		
Monthly income (n=63)				
˃$87	3(17.6%)	14(82.2%)	4.7(.71-31.1)	.1
˂$ 87	2(4.3%)	44(95.7%)		
Perceived relative wealth				
Low	3(5.4%)	53(96.4%)	2.7(.6-11.9)	.197
Average	5(13.2%)	33(86.8%)		
Diagnosis				
Mood disorder	6(26.1%)	17(73.9%)	0.82(.15-.44)	.004
Psychotic disorder	2(2.8%)	69(97.2%)		
Duration of illness				
˃5.9 years	3(5.7%)	50(94.3%)	2.3(.52-10.3)	.271
˂5.9 years	5(12.2%)	36(87.8%)		
Antipsychotic regimen				
FGA	1(2.3%)	43(97.7%)	7(.82-59.3)	.074
SGA	7(14.0%)	43(86.0%)		
One additional antipsychotic				

Yes	1(5.3%)	18(94.7%)	1.9(.21-16)	.575
No	7(9.3%)	68(90.7%)		
Mood stabilizers				
Yes	4(16.7%)	66(83.3%)	0.3(.7-1.3)	.112
No	4(5.7%)	86(94.3%)		

Diet

Almost all participants consumed teff as injera and wheat bread daily. Majority consumed lentils or beans daily. Thirty three percent (n=33) consumed meat once weekly. Most participants consumed milk and egg once weekly. Fats and oils were used almost daily by participants. Most participants consumed fruits and vegetables at least once per week. Daily house hold sugars consumption was 39.0% (n=39). Fish, confectionary, spices and beverages were less frequently used. (Table 7)

Table 7: Food frequency habit of the past two months

Food item	Consumption frequency				
	Never	Daily	2-6/week	Once per week	Once per month
Cereals and grains	0	97(97.0%)	3(3.0%)	0	0
Wheat and wheat products	1(1.0%)	81(81.0%)	16(16.0%)	2(2.0%)	0
Roots and tubers	6(6.0%)	23(23.0%)	29(29.0%)	22(20.0%)	20(20.0%)
Dried lentils, beans…	4(4.0%)	58(58.0%)	28(28%)	10(10.0%)	0
meat	9(9.0%)	9(9.0%)	14(14.0%)	33(33.0%)	35(35.0%)
Fish	80(80.0%)	0	2(2.0%)	2(2.0%)	16(16.0%)
Eggs	9(9.0%)	6(6.0%)	7(7.0%)	46(46.0%)	32(32.0%)
Milk, and milk products	21(21.0%)	7(7.0%)	13(13.0%)	33(33.0%)	26(26.0%)
Fats and oils	0	96(96.0%)	3(3%)	1(1%)	0
nuts	81(81.0%)	0	0	7(7.0%)	12(12.0%)
Vitamin a rich fruits and vegetables	17(17.0%)	7(7.0%)	24(24.0%)	21(21.0%)	31(31.0%)

Other fruits and vegetables	9(9.0%)	21(21.0%)	30(30.0%)	36(36.0%)	4(4.0%)
House hold sugars	33(33.0%)	39 (39.0%)	15(15.0%)	0	13(13.0%)
confectionary	37(37.0%)	0	10(10.0%)	19(19.0%)	34(34.0%)
Spices condiments and beverages	83(83.0%)	0	10(10.0%)	7(7.0%)	0

Discussion

The study attempted to compare the prevalence of metabolic syndrome in first and second generation antipsychotics.

As the result shows most of the participants were taking second generation antipsychotics, which reflects the prescribing trend similar to other countries (4). Few participants were on olanzapine (13.0%) because olanzapine was not mostly available during the study period.

In this study, almost none of the participants had baseline evaluation and monitoring for metabolic side effects of antipsychotics, which was also demonstrated in South African and Ethiopian studies (5, 12).

The prevalence of metabolic syndrome in our study was lower (8.5%) compared to other reports from lower -middle income countries like Tunisia where the mean prevalence of metabolic syndrome was 30.0 % (9). Report from India, showed 11.66% prevalence (13) and a study from Palestine showed prevalence of 44.0% (11). This result could reflect the genetic, dietary variation and economic factors. Some of the

participants took antipsychotics only for six weeks; the metabolic abnormalities might not be obvious earlier unless they are followed up. In addition, the diagnostic parameters that were used for this study were not ethnic-/race-specific which could affect the outcome.

The study shows that, being female was significantly associated with presence of metabolic syndrome, which is similar to the Palestine study (11)

The prevalence of metabolic syndrome in SGA group was higher compared to FGA group, albeit non-significantly, which is similar to other reports. A systematic review and meta-analysis showed the relative risk of developing diabetes in schizophrenic patients taking second generation compared to patients taking first generation antipsychotics was 1.32. (7).

There was limited indication in this study that older age, higher education, being employed, monthly income above $87 and average perceived relative wealth may contribute to the occurrence of metabolic syndrome. However, these were not statistically significant and might be due to the smaller sample size.

In this study the risk of metabolic syndrome was significantly higher for participants with the diagnosis of mood disorder. In two studies the rate of metabolic syndrome in patients with bipolar and schizophrenia were similar (8, 17). The increased risk of

metabolic syndrome for participants with a diagnosis of mood disorder could be due to the trend of prescribing second generation antipsychotic for this patient group.

Taking one additional antipsychotic was associated with presence of metabolic syndrome. A study has reported that compared with antipsychotic monotherapy, polytherapy was associated with elevated rates of metabolic syndrome (20).
In this study abnormal blood pressure, abdominal obesity, abnormal lipid profile and abnormal blood sugar level were not associated with receiving second generation antipsychotics. Most evidence shows that the risk of developing MS is higher with taking SGAs compared to FGAs (7). The Spain study showed more weight gain and abnormal triglyceride level were associated in patients receiving SGA (14). Another study showed patients taking SGAs are more prone to abnormalities in glucose homeostasis but no difference on MS profiles between patients using FGA, SGA, or combination therapy (18). Despite the clear evidence that antipsychotic drugs are implicated in metabolic disease in patients with schizophrenia, there is increasing evidence that schizophrenia itself is an independent risk factor, Prospective studies are needed to explore the precise relationship between antipsychotic drugs, glucose homeostasis, obesity and the metabolic syndrome.

Mood stabilizer co-treatment was not significantly associated with presence of metabolic syndrome which was similar in other study (8). This finding might suggest a susceptibility to antipsychotic-related metabolic dysregulations that is not primarily related to concomitant mood stabilizer treatment.

Though not significant, longer duration of illness was associated with metabolic syndrome. A study showed that metabolic abnormalities were already present in first-episode patients, and considerably increased with increasing duration of illness (19), which suggests a direct impact of the illness and/or negative metabolic side-effects of antipsychotic medication.

Limitations

The study has several limitations. Laboratory tests were not available for all participants.

Some participants only received antipsychotics for 6weeks, which might have contributed to lower prevalence. Questions about income and diet were sensitive issues for the participants.

Most participants were on hospital diet which may not reflect their actual diet.

The participants were all inpatients which could affect the generalizability.

Conclusion and recommendation

The study indicates that metabolic syndrome may be increased in those taking SGAs. Although the overall prevalence of metabolic syndrome is low at this stage, proper screening and monitoring should be a part of the day to clinical practice. Future large scale prospective studies are needed to establish the clear relationship between antipsychotics and cardiometabolic risk factors.

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21 The World Bank. Country and leading groups data 2015

Appendix

Participant consent form

Participant consent form

My name is _____ **.** I would like to invite u to participate in our study, which focuses on side effects of antipsychotic medication, mainly weight gain, change in blood sugar and cholesterol level. We will measure your weight, height and waist circumference and there is also a laboratory test to determine your sugar and cholesterol level. We will inform you the results and recommend management accordingly.
Participating in this study will only depend on your decision to do so and you have all the rights to withhold information, refuse or drop out of the study any time you want without any need to explain to anyone. Withdrawing from the study will have no effect on you. All the information you give during the study will be kept confidential.
You have all the right to ask and get clarification at any time. In case you have doubts or questions.

I would like to confirm your agreement by signing your name if you agree.

Signature of family _____ Date_____

QUESTIONNAIRE

Card number _____

Setting Inpatient ☐ Outpatient ☐

Source of information

Medical record ☐ Participant ☐

Informant ☐ Other, specify _____

Demographic data

1) Age_____
2) Gender 2.1) Male 2.2) female
3) Address: region _____ District _____ Kebele_____
4) Marital status

4.1 Married 4.2 Single

4.3 Cohabitation 4.4 Separated

4.5 widowed 4.6 Divorced

4.7 other, specify _____

5) Highest level of education _____

6) Occupation

6.1 Jobless 6.2 unskilled laborer

6.3 skilled laborer 6.4 farmer

6.5 private business 6.6 pensioner

6.7 student 6.8 house wife

6.9 civil servant 6.10 others, specify_____

7) Income and economic status

7.1) Monthly income of family if living with family (or own if living alone or with his own family) _____

7.2) Compared to others in the neighbourhood, how do you describe your wealth? (This could be the wealth of your family).

7.2.1) Low

7.2.2) Average

7.2.3) Above average

B) Clinical data

1) Diagnosis_____
2) Duration of illness_____
3) Presence of medical illness
   3.1 Hypertension 3.3 Cardiac illness
   3.2 Diabetes 3.4 others, specify _____
4) Family history of medical illness
   4.1 Hypertension 4.3 Cardiac illness
   4.2 Diabetes 4.4 others, specify_____
5) Name of antipsychotic she/he on and the dose_____
6) Duration of the current antipsychotic she/ he is on_____
7) Previous antipsychotic she/he is on_____
8) Additional psychotropic medication

Name _____ Dose_____ duration

_____

Name _____ Dose_____ duration

_____

Name _____ Dose_____ duration

_____

9) Weight in Kg_____

10) Height_____

11) Waist circumference (at the level of the umbilicus) _____

12) BP_____

Laboratory data

1) Fasting blood sugar_____
2) Fasting serum triglycrides_____
3) Fasting HDL_____

ETHIOPIAN FOOD FREQUENCY HABBIT QUESTIONNAIRE

Section of questionnaire used for food frequency recall, by major food groups in the Ethiopian Food consumption Survey. Please ask about the consumption of the food groups listed in the table. Record the frequencies on which the subject has eaten foods from these food groups in the **past two months**.

Food item	code	Consumption 0=no, 1= yes	Consumption frequency	Mode of consumption
Cereal and grains, maze ,teff ,rice & rice product, barely millet, etc	1			
Wheat and wheat product such as bread, wheat flour etc	2			
Roots and tubers(cassava, sweat potato yam potatoes, etc	3			
Dried lentils, beans, peas and other pulses& pulse product(soya meat)	4			
Meat(chicken, beef, goat, calf liver, pork) or meat product (packed/canned meat)	5			
Fish(fresh, dried & canned)	6			
eggs	7			
Milk & milk powder, crud, yogurt, cheese, etc	8			
Fats and oils	9			
Nuts(coconut, groundnut, cashew nut	10			
Vitamin A rich fruits and vegetables such as mango, papaya, pumpkin, carrot, kale, lettuce ,spinach, cauliflower etc	11			
Other fruit and vegetables such as avocado, orange, broccoli, tomato, banana, onion , beet root etc (fresh or canned	12			
Hose hold sugars	13			
Confectionary(ice cream, candy, chocolate, biscuits, cakes	14			
Spices condiments and beverages such as salt sauce cardamom, etc	15			

* **0** = Never
1 = Daily
2 = Two to six days/week
3 = Once weekly
4 = Once monthly
5 = Once every 3 months
6 = Special occasions

****0** = Raw
1 = Cooked
2 = Roasted
3 = As bread
4 = As Injera
5 = As porridge
6 = As sauce
7 = Others…